Abstract

Microbial lung infections are the major cause of morbidity and mortality in the hereditary metabolic disorder cystic fibrosis (CF), yet the molecular mechanisms leading from mutated CF Transmembrane Conductance Regulator (Cftr) to lung infection are still unclear. Here, we show that ceramide age-dependently accumulates in the respiratory tract of uninfected CF-mice due to an alkalinization of intracellular vesicles in *Cftr*-deficient cells that results in an imbalance of the activities of acid sphingomyelinase (Asm) cleaving sphingomyelin to ceramide, and acid ceramidase consuming ceramide. Accumulation of ceramide causes CF-mice to suffer from constitutive age-dependant pulmonary inflammation, death of respiratory epithelial cells, deposits of DNA in bronchi and high susceptibility to develop severe *Pseudomonas aeruginosa* infections. Partial inhibition of Asm in $Cftr^{-/-}/Smpd1^{+/-}$ mice or by pharmacological treatment of CF-mice with the Asm blocker amitriptyline normalizes pulmonary ceramide and prevents all pathological findings including susceptibility to infection. These data suggest inhibition of Asm as a novel treatment strategy in CF.